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Management of Parkinson's Disease

Combined Therapy with Levodopa and Thalamotomy

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An increasing number of parkinsonian patients in whom levodopa fails to relieve tremor are being referred for thalamotomy. The literature suggests that in as many as 50 percent of patients treated with levodopa, there is no relief of tremor because of refractoriness to the medication or intractable side effects which limit dosage. Thalamotomy abolishes contralateral tremor in 90 percent of patients, with an associated mortality rate of 1 to 2 percent and morbidity of 6 percent. The relative merits and complications of levodopa and thalamotomy were reviewed and a therapeutic regimen designed in which the two approaches to treatment are combined to most effectively deal with all the symptoms of parkinsonism.

SINCE THE INTRODUCTION of levodopa, few parkinsonian patients have been treated with surgical procedures in the thalamus. However, initial enthusiasm with levodopa therapy[1-3] has been tempered in the light of long-term studies involving large series of patients. The relative refractoriness of tremor to levodopa and intractable side effects of the medication combine to produce a large number of patients who remain disabled by tremor. This has been reflected in a growing number of referrals of levodopa "treatment failures" for thalamotomy. Our experience and a survey of the literature suggest a need to reappraise the roles of thalamic operation and levodopa in the treatment of parkinsonism.

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Reports of Cases

Following are several representative case reports of parkinsonian patients referred by their neurologists for thalamotomy following an extensive trial of levodopa. In each case stereotaxic ventrolateral cryothalamotomy was done at the University of California, Los Angeles (UCLA) Hospital by one of us (RWR).

CASE 1. A 56-year-old, right-handed Caucasian man had an 11-year history of severe left-sided tremor and rigidity. A three-year course of levodopa, 4 grams per day, produced moderate symptomatic improvement, but resulted in the development of right-sided choreoathetoid movements. In spite of a reduction in the levodopa dose, dyskinesia increased in severity and prevented achievement of therapeutic levels. The patient had been unable to work for the past two years because of tremor, and progressive bradykinesia, dysarthria and dysphagia developed.

At the time of admission to UCLA Hospital in September of 1972, there was pronounced rigidity and constant resting tremor of the left arm and leg. Mild rigidity and intermittent tremor related to emotion were present on the right side. There were intermittent choreiform movements of the right shoulder, masklike facies, blunting of affect, dysarthria and slowing of gait. Mild hypertension (a blood pressure of 140/80 mm of mercury) was well controlled with medication.

Because the levodopa-induced dyskinesia prevented adequate control of tremor, the patient's neurologist referred him for consideration of thalamotomy. A right ventrolateral cryothalamotomy was done under local anesthesia and dexamethasone was used to limit postoperative edema. The procedure produced a 75 percent reduction in rigidity and abolished the tremor on the left. There were no postoperative neurologic deficits. The referring neurologist felt that the procedure had had an excellent result. Levodopa was to be continued at 1.5 grams per day for control of postural and right-sided symptoms. There was no change in the postoperative result on follow-up after 1½ years.

CASE 2. A 50-year-old, right-handed man, a minister, presented with a five-year history of Parkinson's disease manifest primarily as right-sided tremor and rigidity, with dysphagia and akinesia. A regimen of amantadine, trihexyphenidyl and levodopa, 4 grams per day, had resulted in major improvement in all symptoms except tremor, which remained severe and interfered severely with the patient's duties as a minister. Consequently, he was referred for thalamotomy.

On physical examination at admission, normal mental status and mild slowing of speech were noted, but there was no functional gait impairment. There was pronounced rigidity and constant tremor of right arm and leg, exacerbated by anxiety. No left-sided tremor or rigidity was present. Myerson and snout reflexes were positive.

A left ventrolateral thalamotomy was done in January 1971 under local anesthesia with postoperative administration of steroids. There were no postoperative complications. Rigidity was greatly reduced in the right arm and leg, and the patient became essentially free from tremor except for rare tremor during emotional stress. He was continued on levodopa, 1.5 grams per day, for control of bulbar symptoms. The tremor had not recurred at follow-up of three years.

CASE 3. Parkinson's disease first developed 15 years ago in a 61-year-old, right-handed man, a tailor. The disease was initially manifest as right-sided tremor and mild speech disturbance, unresponsive to medications available at the time. Left cryothalamotomy done in 1965 resulted in complete relief of the right-sided tremor, but two years later tremor involving the left arm and leg and severe gait disturbance developed. Treatment with levodopa was begun in 1970 and for several months the left-sided tremor was almost completely relieved, only to recur and become increasingly more severe in spite of maximal doses of levodopa in combination with amantadine. The tremor was disabling for the patient when dealing with customers in his tailor shop.

The patient was admitted to UCLA Hospital in September, 1971 for cryothalamotomy. On examination, mild deterioration of memory, slowing of speech, severe left arm and leg tremor (especially with anxiety) and moderate rigidity on the left side were noted. There was mild right-sided rigidity but no tremor. In addition, there was systolic hypertension (a blood pressure of 180/95 mm of mercury), asymptomatic mitral insufficiency and bilateral femoro-popilateral occlusive disease with absent lower extremity pulses.

Although hypertension and cardiovascular disease imposed increased risks, tremor was sufficiently disabling that cryothalamotomy was done. In spite of postoperative administration of dexamethasone, there was a transient period of mild hemiparesis and confusion. However, this cleared completely within five days and at the time of discharge the patient was free of tremor and there was pronounced improvement in left-sided rigidity. Administration of levodopa was not resumed postoperatively and the patient remains tremor-free 2½ years postoperatively.

CASE 4. A 66-year-old, right-handed housewife presented with an eight-year history of bilateral upper extremity tremor, more severe on the right side. Rigidity and bradykinesia were of minor significance. The tremor was unresponsive to available medical therapy, and in 1966 a left cryothalamotomy was done. There was complete and lasting relief of right-sided tremor, although the left arm and leg tremor became progressively more severe.

A trial of levodopa produced initial relief, but the tremor recurred and intractable nausea plus severe dystonic posturing of the left shoulder limited the dose of levodopa. Administration of

levodopa was tapered to reduce the side effects and eventually it had to be discontinued. Virtually all other available anti-parkinsonian drugs were tried and proved to be ineffective in treating the tremor.

The patient was admitted to UCLA Hospital in August, 1971 for thalamic operation. On physical examination, moderate rigidity and severe resting tremor involving the left arm and leg were seen, as well as dystonic posturing and occasional athetoid movements of the left wrist and hand. Minimal rigidity was present on the right, but tremor was not observed. Gait was festinating, affect was flattened and there was mild dementia and speech disturbance. In August, 1971 a right cryothalamotomy was done with excellent relief of tremor and no postoperative neurologic complications. When seen one year postoperatively, the patient was tremor-free; administration of levodopa was continued for control of gait disturbance.

CASE 5. A 64-year-old, right-handed woman, a cook, presented with three-year history of bilateral tremor, more prominent on the left, and slowing of gait. Initially, a good response was obtained with administration of trihexyphenidyl and amantadine, but relapse occurred. An 18-month trial of levodopa in maximal doses also produced only temporary remission. At the time of admission to hospital the patient was having great difficulty coping with her responsibilities as a cook in a local school because of tremor.

On physical examination in January, 1972, severe resting tremor, involving the left arm and leg, and moderate left-sided rigidity were noted. Occasional tremor was present on the right, particularly with emotion, but tone was only mildly increased. Gait was mildly impaired; speech and mental status were normal.

A right cryothalamotomy was done which completely relieved the contralateral tremor and greatly improved the rigidity. Truncal and bulbar involvement were minimal in this patient; therefore levodopa was discontinued postoperatively. At follow-up after 1½ years, the patient remains free from tremor.

Discussion

Now that sufficient time has elapsed to allow for critical reappraisal, the role of levodopa in the treatment of symptoms of Parkinson's disease may be reassessed and compared with the results of thalamotomy.

The therapeutic efficacy of levodopa in parkinsonism is well established. Generally, about two thirds of the patients treated with levodopa experience a pronounced symptomatic improvement,[4-8] but the remaining 30 percent show little or no benefit. Not all of the symptoms of parkinsonism are equally responsive. Although it is generally accepted that levodopa is the best agent available for the relief of bradykinesia and autonomic effects,[4-8] and is very effective in relieving rigidity, tremor is significantly less responsive, even at very high doses. Cotzias,[1] and Calne[5] in a review of the literature, note that levodopa is least effective in treatment of tremor. Langrall[6] in a study of 1,600 patients found an improvement in bradykinesia in 71 percent of the patients, and in rigidity in 70 percent. However, limb tremor was improved in 59 percent of the patients and an improvement in tremulous handwriting occurred in only 25 percent. Others have found that about one third of the 60 to 70 percent of patients in whom levodopa is effective in treating akinesia and rigidity show no improvement in tremor.[5,7,8] That is, less than half of the parkinsonian patients treated with levodopa alone had significant relief of tremor. As reported by Cotzias[1] and Markham,[7] and exemplified in the cases reported here, tremor which initially improved on levodopa therapy may recur and become refractory to long-term treatment.

Levodopa Side Effects

Side effects to therapeutic dosages are an important factor in limiting the overall effectiveness of levodopa. Side effects occurred with a frequency of 92 percent in Langrall's study of 1,600 patients.[6] In the majority of patients these reactions consisted of nausea, insomnia or confusion and were transient or, at worst, tolerable accompaniments to the therapeutic benefit. However, in as many as 30 to 50 percent of the patients side effects developed during the course of therapy which were serious enough to limit dosage or require cessation of treatment.[4-7]

Cardiac arrhythmias and postural hypotension have been related to levodopa in 7 to 30 percent of patients;[3,5,9] only a few fatalities have been reported.[5] Psychiatric side effects were seen in 20 to 30 percent of patients treated.[3,10-12] These included intellectual deterioration,[13] confusion, depression, psychosis and even occasional suicides.[3,10-12]

The problem of levodopa-induced involuntary movements was particularly disturbing, occurring

in 30 to 80 percent of patients.[3,5,7,8,14,15] These choreoathetoid or dystonic movements involving tongue, head or proximal limb muscles were generally dose-related. More bizarre motor disturbances have been reported in some patients on levodopa. Barbeau[15] found that 10 percent of patients developed an "akinesia parodoxica" in which a sudden hypotonia and hypotension rendered patients temporarily unable to move and which resulted in falls that often produced hip fractures. A peculiar "on-off" effect has been described that may produce abrupt swings from nearly complete remission to severe tremor, rigidity or choreoathetosis several times per day.[6,15] Transient unexplained comas lasting 1 to 24 hours have been reported.[3,16] These observations have prompted Barbeau to suggest that "after a while the metabolism of brain dopamine is modified" by levodopa.[15] Other alterations in brain chemistry have been reported.[17] Although yet to be established, there is some experimental evidence to suggest that levodopa induced dyskinesias may be related to cerebellar infarcts which have been demonstrated in animals on levodopa.[18] No significant toxic effects to the administration of levodopa have emerged to date, but minor abnormalities of laboratory values are found in a high percentage of patients.[5,6] There is increasing evidence that levodopa has metabolic side effects, including alterations in glucose metabolism and trophic hormone levels.[19]

Thus, troublesome side effects, unexplained refractory states and differential effectiveness are emerging as increasingly important limitations on the benefits derived from levodopa therapy. As a result, a growing number of patients are again being referred for thalamotomy to treat tremor and rigidity after levodopa has failed to produce satisfactory results.

Ventrolateral Thalamotomy

The value of ventrolateral thalamotomy in Parkinson's disease has been well documented since 1955. When the thalamic lesion is confined to the ventrolateral nucleus, immediate and lasting relief of contralateral tremor and, to a lesser extent, rigidity occurs in 70 to 90 percent of patients, depending on the criteria for patient selection.[20-23] In a series reported by Cooper,[20] in which he analyzed the results of 1,001 cryogenic thalamotomies done in 1963, tremor was completely relieved in 90.6 percent of patients, and improved in an additional 9 percent; there was no significant return of tremor in a mean follow-up of ten months. Ojemann and Ward[24] have shown that the improvement in tremor remained stable in 40 percent of patients with follow-ups as long as ten years, while disease in the opposite limbs and trunk continued to progress (the long-term efficacy of levodopa is yet to be established). Contralateral rigidity is 75 to 100 percent improved in two thirds of patients.[20-23]

The patients most likely to have excellent relief of tremor and rigidity with thalamotomy are those in whom involvement is primarily unilateral, with little bradykinesia, dysarthria or autonomic symptoms.[20,22] However, more than half of the patients with severe bilateral symptoms, including autonomic and bulbar dysfunction, can expect pronounced improvement in contralateral tremor and rigidity following thalamotomy.[22]

Bradykinesia generally does not respond to thalamotomy, although Ojemann and Ward[24] report some element of improvement in bradykinesia manifest as finger dexterity in 70 percent of their patients. Bulbar and autonomic symptoms of parkinsonism are essentially unaffected by thalamotomy.

The risks of stereotaxic thalamotomy have progressively decreased with the refinements of technique and experience in case selection of the past decade.[25] Overall mortality rates in large series are now less than 2 percent.[21-23,25-27] Death directly attributable to the procedure is usually a result of intracerebral hemorrhage, and occurs in 0.6 percent of patients.[20] The risk of fatal hemorrhage appears to be related to the degree of cerebral arteriosclerosis, as the mortality rate is zero in patients under 50 years of age, but increases to 1.9 percent by age 70 years, and 7.4 percent in patients with hypertension.[20] Systolic hypertension which is not readily controllable with medication is not considered a contraindication to stereotactic surgery. The remainder of the postoperative deaths are related to the effects of pulmonary emboli, myocardial infarcts and the like.

Postoperative Neurologic Complications

The most common postoperative neurologic complications have been imbalance, confusion and mental changes, speech disturbance and hemiparesis. In a review of the literature, Cooper[26] found that these complications occur in 5 to 20 percent of operations, but they are generally transient effects in the immediate postoperative period. Permanent neurologic complications following unilateral operations occur with a fre-

quency of 2 to 6 percent.[26,27] The age of the patient, the severity of the parkinsonism, the presence of other medical diseases and the surgical technique (including the number of lesions) appear to be the most important factors in the morbidity resulting from thalamic surgery.[25] The risk of speech disturbance is increased with dominant hemisphere lesions, and may be as high as 5 to 33 percent with bilateral stereotactic operation.[20,22,24,28,29]

Two technical developments have notably diminished the frequency of neurologic complications. Cryogenic stereotactic probes enable the surgeon to examine the patient for desired relief of tremor, as well as avoidance of complications, while the thalamic target is cooled under local anesthesia. If undesirable neurologic effects are produced, the probe is rewarmed immediately with completely reversible results. The use of dexamethasone in the immediate postoperative period greatly diminishes the incidence and severity of transient neurologic deficits that result from the edema surrounding the thalamic cryogenic lesion.

Hoehn and Yahr[30] have reported a study of the natural history of Parkinson's disease in 802 patients. They found tremor was the most common presenting symptom. In spite of control of tremor with thalamotomy and medications other than levodopa, the disease, as manifest by autonomic and bulbar effects and intellectual deterioration, continued to progress. After five years, one quarter of the patients were disabled or dead and after 10 to 14 years, 80 percent were disabled or dead. The principal causes for increased mortality, which was three times greater than the norm, were pneumonia and urinary infections as complications of the disease. The mortality associated with the disease thus must be weighed against the risks involved in thalamotomy or levodopa therapy. It is yet to be determined whether levodopa, through improvement in akinesia and autonomic effects, may alter the mortality and disability pattern of parkinsonism.

Therapeutic Regimen

With these considerations in mind it seems reasonable to propose the following regimen in the treatment of parkinsonian symptoms. In the majority of patients who present initially with a combination of bilateral rigidity, bradykinesia and tremor, a trial of levodopa and other medications is indicated for a period of 12 to 18 months. Of these patients, a group will emerge in whom tremor is not improved by levodopa. This group will be composed of the patients in whom therapy is limited by intractable side effects, and the patients in whom tremor shows little response to levodopa. According to the literature, this may amount to more than half of those treated with levodopa.[4-8] These patients should then be considered for thalamotomy by weighing the functional disability created by the unrelieved tremor and rigidity against the factors which may substantially increase surgical risk. Following thalamotomy, it is expected that the patients will continue to require levodopa for management of akinesia, autonomic symptoms and unilateral limb involvement. As reported by Hughes et al[32] in a double blind study, and confirmed by others,[11,33] patients who have had thalamotomies show no difference in the response of parkinsonian symptoms to levodopa than do those patients who have not had previous thalamotomy. Indeed, there appears to be a beneficial effect in that there is a lower incidence of levodopa induced dyskinesias following thalamotomy.[31]

Early in the course of parkinsonism, tremor is the most prominent symptom.[30] In a small group of patients, the disease may appear self-limited to tremor and rigidity of one or two limbs.[24,31] In these patients, if tremor is not relieved soon after achieving therapeutic dosage of levodopa, thalamotomy may be more strongly recommended. This is the group of young parkinsonian patients in whom the risks of thalamotomy are lowest, and in whom relief of tremor can be predicted in 90 percent. Many of these patients, of course, will eventually develop tremor and rigidity involving the opposite limbs. Bilateral staged thalamotomies involve additional risks, but can be done safely in well-selected patients (Case 4). For those patients who progress to akinesia and autonomic disorders, levodopa will again be required.

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